SCIENCE CHINA
Life Sciences

SPECIAL ISSUE: Non-coding RNAs
• REVIEW •
Progress of Projects Supported by NSFC

October 2013 Vol.56 No.10: 944–952
doi: 10.1007/s11427-013-4546-5

ADAR-mediated RNA editing in non-coding RNA sequences

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Received July 7, 2013; accepted August 20, 2013; published online September 3, 2013

Adenosine to inosine (A-to-I) RNA editing is the most abundant editing event in animals. It converts adenosine to inosine in double-stranded RNA regions through the action of the adenosine deaminase acting on RNA (ADAR) proteins. Editing of pre-mRNA coding regions can alter the protein codon and increase functional diversity. However, most of the A-to-I editing sites occur in the non-coding regions of pre-mRNA or mRNA and non-coding RNAs. Untranslated regions (UTRs) and introns are located in pre-mRNA non-coding regions, thus A-to-I editing can influence gene expression by nuclear retention, degradation, alternative splicing, and translation regulation. Non-coding RNAs such as microRNA (miRNA), small interfering RNA (siRNA) and long non-coding RNA (lncRNA) are related to pre-mRNA splicing, translation, and gene regulation. A-to-I editing could therefore affect the stability, biogenesis, and target recognition of non-coding RNAs. Finally, it may influence the function of non-coding RNAs, resulting in regulation of gene expression. This review focuses on the function of ADAR-mediated RNA editing on mRNA non-coding regions (UTRs and introns) and non-coding RNAs (miRNA, siRNA, and lncRNA).

RNA editing, non-coding sequence, ADAR, gene regulation

Citation: Yang Y, Zhou X X, Jin Y F. ADAR-mediated RNA editing in non-coding RNA sequences. Sci China Life Sci, 2013, 56: 944–952, doi: 10.1007/s11427-013-4546-5

Protein-coding genes account for only 1% of the mammalian genome, yet 70%–90% of the rest of genome can be transcribed [1]. Therefore, in mammalian cells, most of the transcriptome consists of non-coding RNA sequences, which include untranslated regions in pre-mRNA such as 5′- and 3′-untranslated regions (UTRs) and introns, highly abundant and functionally important RNAs such as transfer RNA (tRNA) and ribosomal RNA (rRNA), small non-coding regulatory RNAs such as microRNA (miRNA), small interfering RNA (siRNA), and piwi-interacting RNA (piRNA), long non-coding RNAs (lncRNA) such as Xist and HOTAIR, and other RNAs such as small nuclear RNA (snRNA) and small nucleolar RNA (snoRNA). These features are involved in translation [2–6], pre-mRNA splicing [5,7–9], gene regulation [6,10–12] amongst other activities. As with proteins, disorder of the non-coding RNAs can result in many diseases, including cancer [13–15], Prader-Willi syndrome [16,17], autism [18,19], and Alzheimer's disease [20].

RNA editing is an important form of post-transcriptional processing, which can alter RNA molecules by nucleotide modification, insertion, or deletion [21]. In animals, the most common editing event is adenosine to inosine (A-to-I) RNA editing, which converts adenosine to inosine in double-stranded RNA (dsRNA) regions through the action of adenosine deaminase acting on RNA (ADAR) enzymes [22]. Recent RNA-Seq data shows there are 22688 RNA editing events in human non-coding RNAs, introns, UTRs, and

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protein-coding sequences. Approximately 93% of these editing sites convert adenosine to inosine, consistent with known A-to-I RNA editing [23]. Inosine is recognized as guanosine in protein-RNA interfaces and base pairing. Thus, editing in coding regions can lead to codon change, resulting in increased diversity of protein isoforms and function [24,25], while in non-coding regions of pre-mRNA or non-coding RNAs, it can affect pre-mRNA splicing, mRNA translation, and small non-coding RNA processing. In this review, we will briefly introduce ADAR-mediated RNA editing in non-coding regions of pre-mRNA and non-coding RNAs.

1 A-to-I RNA editor genes: *ADAR* and *ADAT*

A-to-I RNA editing converts adenosine to inosine by hydrolytic deamination of the adenine base [26,27]. The deamination reaction is catalyzed by two different kinds of enzymes: adenosine deaminases that act on RNA (ADAR) and adenosine deaminases that act on tRNA (ADAT). ADAR specifically acts on dsRNAs [26–31], while ADAT is a tRNA-specific adenosine deaminase [32–36].

ADARs are believed to exist in all Metazoa [37]. In *Caenorhabditis elegans*, two ADARs exist, *CeADR1* and *CeADR2* [38] (Figure 1A). However, only one ADAR gene, *dADAR*, is present in *Drosophila melanogaster* [39] (Figure 1A). There is also only one *ADAR* in squid, which can generate two different splicing isoforms [40] (Figure 1A). Three ADARs (*ADAR1*, *ADAR2*, and *ADAR3*) are present in vertebrates [41,42] (Figure 1A). All ADARs have 1–3 dsRNA binding domains and one deaminase motif. Furthermore, *ADAR1* contains two Z-DNA binding domains [43], and *ADAR3* contains an R domain (arginine-rich single-stranded RNA binding domain) [29] (Figure 1A). *ADAR1* and *ADAR2* are believed to have arisen in early metazoan evolution from *ADAT*, while *ADAR3* might have originated in vertebrates [37]. In addition, *ADAR1* or *ADAR2* may have been lost in several species, such as insects and squid [37].

ADARs were discovered as dsRNA-specific adenosine deaminases [26–31]. They are not sequence specific; binding sites occur along the entire sequence of perfectly paired dsRNAs. Thus these molecules are edited non-selectively, and up to 50% of adenosine residues can be converted to inosine [44,45]. However, most of the known editing substrates of ADARs are imperfectly-paired dsRNAs. These substrates are invariably interrupted with loops, bulges, and mismatches [46], and it is thought that these RNA structural features promote the selectivity of ADARs [44]. Research also shows that the RNA tertiary structure is important for the recognition of editing sites [47,48]. In addition, the solution structure of the ADAR2 double-stranded RNA-binding motifs (dsRBM)-RNA complex reveals that

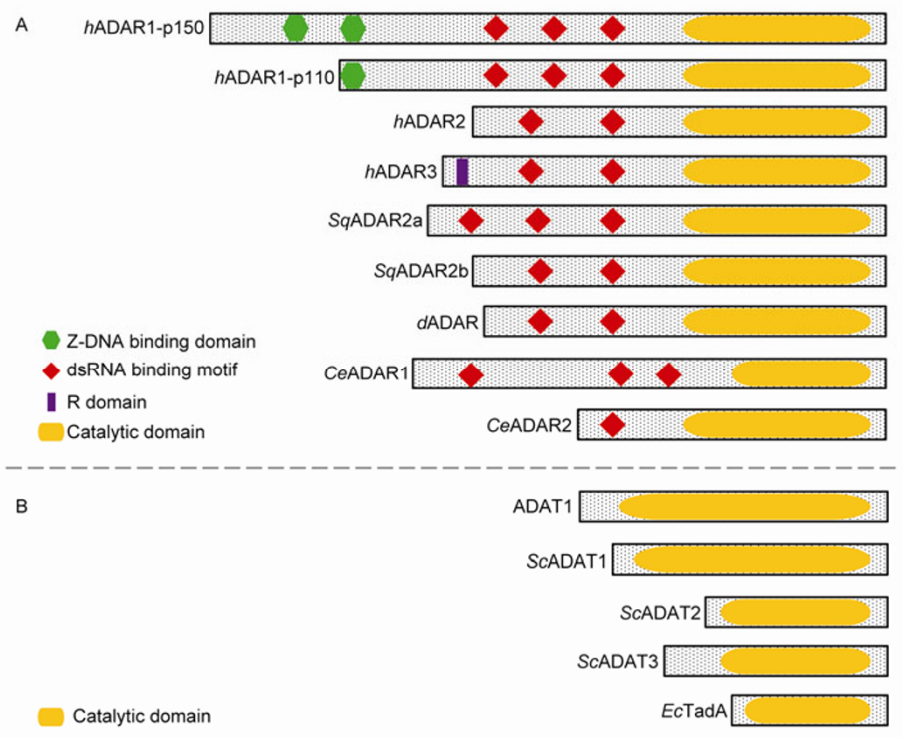

Figure 1 ADAR and ADAT family. A, Human (*h*ADAR1-p150, *h*ADAR1-p110, *h*ADAR2, and *h*ADAR3), squid (*Sq*ADAR2a and *Sq*ADAR2b), fly (*d*ADAR) and worm (*Ce*ADAR1 and *Ce*ADAR2) ADARs are shown with Z-DNA binding domains (green hexagon), R domain (purple rectangle), dsRNA binding motifs (red prism) and catalytic domains (yellow oval). B, Mammalian (ADAT1), yeast (*Sc*ADAT1, *Sc*ADAT2, and *Sc*ADAT3) and bacterial (*Ec*-TadA) ADATs are shown with catalytic domains (yellow oval). No RNA binding motifs were found in ADATs.

ADAR2 dsRBM binding to the GluR-2 R/G editing site depends on structure and sequence [49]. However, the editing-specific structural features are still not defined.

Both ADAR1 and ADAR2 can target perfectly- or imperfectly-paired dsRNAs, resulting in promiscuous or selective A-to-I editing. Although ADAR3 cannot edit any currently known substrate RNAs, it can bind dsRNAs and inhibit the activities of other ADAR enzymes *in vitro* [29,50]. Therefore, some researchers believe it plays a regulatory role in RNA editing [29,50]. Several studies showed that *ADAR1* and *ADAR2* are expressed in multiple tissues, including the brain, heart, and lung; however, *ADAR3* only exists in the brain [29,50–55]. *ADAR1* has two different splicing isoforms, full-length ADAR1-p150, and short-form ADAR1-p110 [56] (Figure 1A). Results have revealed that ADAR1-p150 is mainly stored in the cytoplasm, whereas ADAR1-p110 and ADAR2 are located in the nucleolus [56–59].

ADAT can edit positions-34 and 37 in tRNAs and convert adenosine to inosine, resulting in enlargement of the codon recognition capacity during protein synthesis [21,60,61]. *ADAT* is present in all eukaryotes, but has another name, tRNA adenosine deaminase (*TadA*) in bacterial [62] (Figure 1B). These data indicate that A-to-I editing in tRNAs is conserved between prokaryotes and eukaryotes. ADATs can target tRNAs, but they do not have any known RNA binding motifs. Thus it was reported that the substrate recognition depends on the unique L-shaped tertiary structure of tRNAs [21,61,63].

2 RNA editing in non-coding regions of pre-mRNA

Coding regions of pre-mRNAs are typically subject to selective editing, resulting in codon alteration. Mammalian glutamate receptors and serotonin receptors and *Drosophila* sodium channels are examples of regions with such selective editing [25]. However, most of the pre-mRNA editing sites are in non-coding regions such as UTRs and introns [23,64]. These editing sites are usually non-selectively modified by ADARs. In the following sections, we will focus on editing in non-coding regions of pre-mRNA (Figure 2).

2.1 Editing in UTRs

UTRs in mRNA are associated with mRNA stability, export, and translation. Therefore, editing in UTRs may affect gene expression through nuclear retention, translational regulation, and degradation (Figure 3).

More than 10 years ago, an attractive hypothesis posited that promiscuous A-to-I edited RNAs caused nuclear retention by binding to p54^{nrb}-containing complexes, based on the results of synthetic RNA analysis [65,66]. Several years later, the first endogenous example, mouse CAT2 transcribed nuclear (CTN)-RNA, was found. CTN-RNA is transcribed from *mCAT2*, with a longer 3′-UTR(4.5 kb) than protein coding *mCAT2* mRNA [67]. A large double-stranded region in the CTN-RNA 3′-UTR was hyper-edited [67]. Thus, CTN-RNA was retained in the nucleus, mediated by p54^{nrb}-containing complexes [67]. Under stress conditions, CTN-RNA is cleaved to remove the edited 3′-UTR, and then exported to the cytoplasm for production of mCAT2 protein [67]. Therefore, cells can rapidly produce mCAT2 proteins in response to stress by storing CTN-RNA in the nucleus.

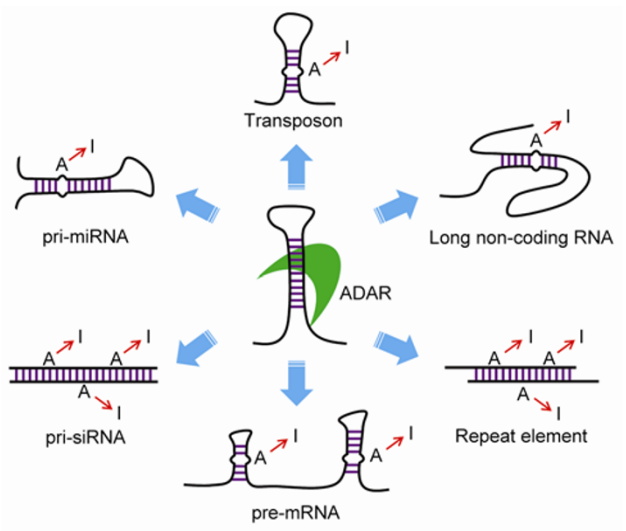

Figure 2 Substrates of ADARs. ADARs contain dsRNA binding motifs, and recognize dsRNAs. In cells, many RNAs can form dsRNAs. There are several known dsRNAs that can be targeted by ADARs, including transposons, long non-coding RNAs, repeat elements, pre-mRNAs, pri-miRNAs, and pre-siRNAs.

Recent research shows that *Nicolin 1* and *Lin28* mRNA both contain a pair of hyper-edited inverted repeat Alu elements (IR*Alus*) in the 3′-UTRs, causing nuclear retention [68,69]. Analysis shows that nearly 300 human genes have highly edited IR*Alus* in their 3′-UTRs [68], indicating that perhaps more genes are regulated by nuclear retention. Additionally, studies have shown that some mRNAs with edited 3′-UTRs are present in the cytoplasm [70,71]. It appears that several mRNAs can escape from hyper-editing-induced nuclear retention. However, the different fates of hyper-edited mRNAs depend on different developmental stages, tissues, or genes. For example, mRNAs containing inverted repeats in their 3′-UTRs were exported to the cytoplasm in human embryonic stem cells, indicated by their lack of paraspeckles [72]. Therefore, there may be other important proteins or non-coding RNAs associated with hyper-editing-induced nuclear retention that is currently unknown.

In UTRs, structural RNA elements such as internal ribosome entry sites, pseudoknots, *cis*-active RNA elements, cap-independent translation enhancer elements, and spliced leaders can regulate mRNA translation [73]. These structural

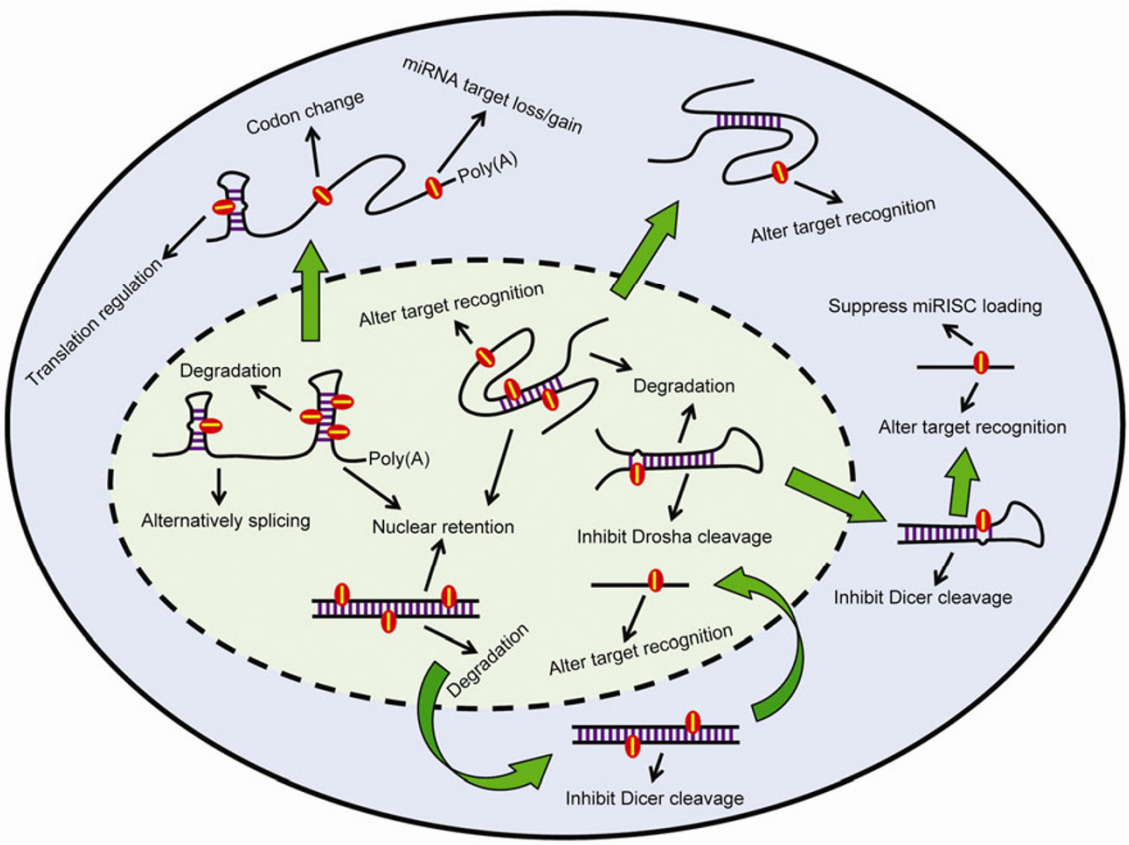

Figure 3 The function of A-to-I RNA editing. Editing of pre-mRNAs can increase protein diversity by codon change and alternative splicing or influence gene expression by nuclear retention, degradation, and translation regulation. However, most of the RNA editing happens in non-coding RNAs, such as lncRNA, miRNA, and siRNA. Editing would affect their stability, biogenesis, and target recognition.

RNAs can interact with RNA binding proteins like polypyrimidine tract-binding protein-associated splicing factor, G-rich sequence factor, and Y-box binding protein 1 [73]. Therefore, it is possible that dsRNA binding proteins, such as ADARs, interact with the structural RNAs [23,64,74,75]. ADARs can convert adenosine to inosine in AC mismatches and create IC pairs to stabilize the double-stranded structures. Thus ADAR-mediated RNA editing may affect the interactions between the structural RNA elements and dsRNA binding proteins, leading to alteration of translational efficiency, initiation, and termination (Figure 3).

Some research shows that the stability and translatability of mRNAs are no different between wild-type *C. elegans* and mutants that lack editing [70]. However, this study only monitored five edited 3′-UTRs by fusing a red fluorescent protein gene in *C. elegans* [70]. In fact, many RNA editing events have been identified in UTRs, especially in mammals [23,64,74,75]. However, the function of these RNA editing sites remains unknown. Perhaps a high-throughput method for analyzing protein expression could help determine whether ADAR-mediated RNA editing affects mRNA translation.

miRNAs can regulate mRNA translation and stability by binding to the miRNA target sites of 3′-UTRs [76]. Computational analysis revealed that a set of RNA editing sites could interrupt miRNA target sites that match seed regions [77]. The study also showed that RNA editing can create new miRNA target sites [77]. Recent analysis indicated that 20% of the editing sites in the 3′-UTRs may alter miRNA target sites [23]. These results suggest RNA editing may regulate gene expression by editing miRNA target sites in 3′-UTRs.

It was reported that Tudor staphylococcal nuclease (Tudor-SN) can bind to and promote cleavage of highly-edited dsRNAs with IU and UI pairs *in vitro* [78,79]. Tudor-SN was identified as an enhancer of cleavage [78], whereas some results show it can cleave inosine-containing RNAs [80]. Hence, the hyper-edited UTRs may be cleaved from mRNAs by Tudor-SN or other nucleases, resulting in mRNA degradation (Figure 3). Alternatively, perhaps Tudor-SN-induced cleavage can remove the hyper-edited 3′-UTR, and release the nuclear retained mRNA to the cytoplasm for translation.

Recently, some results have indicated that Tudor-SN and ADAR1 p150 are co-localized to cytoplasmic stress granules under oxidative stress or transfection of polyinosine-polycytidylic [81,82]. ADAR1 has been reported to have anti-apoptotic functions under stress [83–85]. Thus, ADAR1 p150 may edit target RNAs in the cytoplasm, and the resultant IU-dsRNA may recruit other proteins such as Tudor-SN to format the stress granule in cellular stress responses [81]. These results suggest that ADAR1-mediated

RNA editing may play an important role in cell survival during cell stress. However, more details need to be determined, such as what the target RNAs are and what role ADAR1 plays in cytoplasmic stress granules.

2.2 Editing in introns

Introns have the highest number of RNA editing sites in mRNA molecules [23,64]. However, it is still unclear why so many RNA editing sites are located in introns. One reported function is regulation of pre-mRNA splicing (Figure 3). ADAR2 can edit the proximal 3′ acceptor site of its own mRNA to convert the intronic AA to an Al dinucleotide, resulting in the insertion of 47 nucleotides to the ADAR2 coding region [86]. This insertion changes the reading frame of the ADAR2 transcript, producing a different protein isoform [86]. Similarly, ADAR may also edit a proximal 3′ donor site to convert AU to an IU dinucleotide, leading to intronic nucleotide insertion. Editing can destroy the 3′ acceptor site by changing AG to an IG [87].

Recently, some data showed that editing can cause intronic sequence to exonize by creating a functional 3′ acceptor site (AG) and changing exonic splicing enhancers [88,89]. These results suggest editing may regulate mRNA splicing and play a role in exon evolution, especially in primates. However, we need to confirm if there are other functions of such significant RNA editing in introns.

2.3 Editing in repeat elements

Human genome sequencing shows that 45% of the genome consists of repetitive and transposable elements, such as long interspersed elements (LINEs) and short interspersed elements (SINEs) [90]. Alu is one class of SINE, and it has over one million copies, covering 10% of the whole human genome [91]. Several studies have shown that 90% of A-to-I RNA editing happens in Alu sequences [23,74,75,92–94]. Alu sequences can readily form long dsRNAs, which will be the target of ADARs (Figure 2). Edited Alu sequences in UTRs can cause nuclear retention and affect translation [68,69] and pre-mRNA splicing in introns [86]. Alu sequences are the most abundant class of transposon in humans, so highly-edited Alu sequences may promote genome evolution, such as Alu exonization in primates [88,89]. In *Drosophila*, several editing sites were found around the terminal inverted repeats in the *KP* element, which is one of the deletion derivatives of *P* transposable elements [95]. These results suggest that A-to-I RNA editing may play an important role in the repetitive and transposable elements.

Most of the ADAR substrates are intramolecular dsRNAs, however, some results indicate intermolecular dsRNAs can also be edited by ADARs (Figure 2). In *D. melanogaster*, *4f-rnp* and *sas-10* are located on opposite DNA strands [96]. Their mRNAs can pair to form an intermolecular dsRNA, which will be edited by dADAR [96]. Another example is *eri-6* 5′-UTR or 3′-UTR and *eri-7* 5′-UTR, which are edited by forming an intermolecular dsRNA in *C. elegans* [97]. Interestingly, *eri-6* and *eri-7* mRNA were *trans*-spliced to form an *eri-6/7* mRNA with final function [97]. These results raise the question of whether ADAR-mediated RNA editing is associated with *trans*-splicing, and whether mRNAs with repeat elements are regulated by ADARs.

3 RNA editing in non-coding RNAs

During the past half-century, a large number of non-coding RNAs have been characterized, including tRNAs, rRNAs, small non-coding RNAs, long non-coding RNAs amongst others. Along with the study of non-coding RNAs, many RNA modifications have been characterized in non-coding RNAs, especially in tRNAs [98]. A-to-I editing is one kind of RNA modification in non-coding RNAs. In the following sections, we will focus on A-to-I editing in small and long non-coding RNAs (Figure 2).

3.1 Editing in small non-coding RNAs

miRNA and siRNA are two kinds of important small non-coding RNAs with gene expression regulatory functions [99]. pri-miRNAs can form intramolecular stem-loop structures and be cleaved into smaller pre-miRNAs by Drosha in the nucleus [99]. Following Drosha cleavage, the pre-miRNAs are exported to the cytoplasm and processed into mature miRNA by Dicer [99]. siRNAs are generated from long dsRNAs by Dicer cleavage [99]. The hairpin structures of pri-miRNA or pre-miRNA and long dsRNAs are suitable substrates for ADARs, thus miRNA and siRNA may be edited.

In the nucleus, pri-miRNAs with hairpin structures are processed by Drosha-containing complex [99]. Editing may affect pri-miRNA processing (Figure 3). Studies have indicated that the pri-miR-22 can be edited to generate edited pre-miR-22 [100]. Several editing sites have since been found in pri-miR-142 [80]. These editing sites change AU or UA pairs to a less stable IU or UI, and inhibit Drosha-DGCR8 complex cleavage. Finally the edited pri-miR-142 is degraded by Tudor-SN [80]. Interestingly, the levels of endogenous miR-142-5p and miR-142-3p were substantially lower in wild-type mouse spleens than those in ADAR1$^{-/-}$ and ADAR2$^{-/-}$ spleens [80]. This suggests that miR-142 biogenesis is regulated by ADAR1 and ADAR2.

In the cytoplasm, pre-miRNAs are further processed into mature miRNA by Dicer-containing complex [99]. In this step, editing also can influence pre-miRNA cleavage (Figure 3). Several studies have shown that pri-miR-151 was edited at the minor −1 site and major +3 site by ADAR1 [101]. These two editing sites did not affect cleavage of pri-miR-151 by Drosha-DGCR8 complex, but they inhibited cleavage of pre-miR-151 by Dicer-TRBP complex [101]. A large-scale survey of human pri-miRNA editing showed

that 16% of human pri-miRNAs undergo A-to-I RNA editing, and may affect the Drosha or Dicer cleavage [102]. These findings suggest that A-to-I editing can modulate miRNA biogenesis.

In addition, miRNA processing can also be influenced by ADARs independently of editing. Drosha cleavage of pri-mR-376a2 was inhibited by catalytically inactive ADAR2 because of ADAR2 binding [103]. This result indicates that other dsRNA binding proteins may bind to the pri-miRNA or pre-miRNA hairpin structures and affect the miRNA processing. Recently, it was reported that ADAR1 can interact with Dicer to form heterodimers independently of RNA binding [104]. The heterodimer increases the rate of miRNA and siRNA processing and augments RISC loading and target RNA silencing efficacy [104]. These results suggest ADAR may influence the function and processing of other dsRNAs outside of its editing activity.

A-to-I editing not only affects miRNA processing, but also can influence miRNA function. First, the editing will affect miRNA loading into miRISC (Figure 3). Several editing sites were found in the Epstein Barr Virus-encoded pri-miRNAs in latently EBV-infected cells, and editing suppressed the miRISC loading of miR-BART6-5p [105]. Therefore, it may also affect the miRISC loading of endogenous miRNAs. The editing would then influence miRNA target recognition (Figure 3). Results indicate that miR-376-5p, with or without editing, silences different genes [106], and that more edited mature miRNAs were found in the human brain [102]. These editing sites also may alter miRNA target recognition [102].

Therefore, in general, editing in miRNAs will affect miRNA biogenesis and target recognition.

siRNA differs miRNA, which is derived from long dsRNAs [99]. pri-miRNAs with hairpin structure are often edited in several selective sites, but the long dsRNAs may be randomly and highly edited (up to 50% of adenosine residues converted to inosine) [27,45,107] (Figure 2). As already described in the previous section, the highly-edited dsRNAs will be retained in the nucleus or degraded by Turdo-SN [65–67,78–80] (Figure 3). Long dsRNAs are exported to the cytoplasm, and processed to siRNA by Dicer [99]. Thus, nuclear retention and degradation will reduce siRNA production. AU pairs replaced by IU pairs in pre-miRNA can inhibit Dicer cleavage [101], so highly-edited dsRNAs may inhibit Dicer cleavage (Figure 3). It has been reported that long dsRNAs with 43% A-to-I editing prohibit its processing into siRNA by Dicer *in vitro* [107]. Taken together, these results show that A-to-I editing on long dsRNAs can reduce the production of siRNA.

To determine the relationship between A-to-I editing and RNAi, several *in vivo* studies were established. In *C. elegans*, the impaired chemotaxis phenotype was observed in ADAR-*null* strains, but reverted to wild-type when crossed with RNAi-defective worms [108]. This suggests that chemotaxis is controlled by the balance between A-to-I editing and RNAi. Moreover, another result showed that A-to-I editing prevents somatic transgene silencing by RNAi in *C. elegans* [109]. Interestingly, *in vitro* assays show that ADAR1-p150 can tightly bind to siRNA, and ADAR1-p150 prohibits RNAi in mouse embryonic fibroblasts [110]. These studies indicate that A-to-I editing can influence RNAi silence *in vivo*.

RNAi silencing gene expression is believed to be an innate immune defense response against viruses [111–117]. However, several studies show high doses of siRNA induce *ADAR1* expression and reduce the RNAi efficiency in mice [118]. This suggests that the *ADAR1* gene may play a negative feedback role in RNAi. Although there is a consensus regarding the regulatory function of ADARs in RNAi, there is still an important question that needs to be addressed: Is the regulation of ADARs dependent on editing activity?

3.2 Editing in long non-coding RNAs

Long non-coding RNA accounts for a large fraction of the transcriptome, and thousands of lncRNAs have been found in recent years [119–121]. Many lncRNAs are believed to have secondary folds, which may be the substrates for ADARs [122]. Moreover, natural antisense transcripts that are transcribed from the antisense strand of protein coding genes may pair with sense transcript 5′- or 3′-UTRs and be edited by ADARs [96,97] (Figure 2). In addition, Alu RNAs can form intramolecular stem-loop structures or long intermolecular dsRNAs, and a set of studies indicate that many edited Alu sequences are found in the human transcriptome [23,74,75,92–94]. Recent high throughput RNA-Seq shows lncRNAs such as *Jpx* and *Malat 1* can be edited at several sites in the human transcriptome [23].

Although edited lncRNAs have been reported, their function remains unclear. There are several potential functions for the edited lncRNAs. First, highly-edited lncRNAs, such as CTN-RNA, can be retained in the nucleus (Figure 3) [67]. Following cleavage of the hyper-edited 3′-UTR, CTN-RNA was exported to cytoplasm for translation under stress [67]. Therefore, edited lncRNAs may be retained in the nucleus, and exported to the cytoplasm following cleavage of the hyper-edited regions. Second, edited lncRNAs may be degraded by Tudor-SN, like edited miRNA [80] (Figure 3). Thus, A-to-I editing may be a negative feedback mechanism to regulate lncRNAs. Third, editing may alter the target sites of the lncRNAs. lncRNAs can interact with RNA or DNA by base pairing [122–125] (Figure 3). Therefore, the edited and non-edited transcripts may pair with different targets. Finally, ADARs may compete with other RNA binding proteins for binding to lncRNAs, especially dsRNA binding proteins (Figure 3). Much evidence exists to show that lncRNAs can interact with many RNA binding proteins [1,120,122], and ADARs may bind to the double-stranded regions of lncRNAs. This may prohibit other dsRNA binding proteins from interacting with lncRNAs and affect the lncRNA function. In general, ADARs may play an im-

portant regulatory role in lncRNA function, either dependent on or independent of editing activity.

4 Prospects and conclusion

A-to-I RNA editing is believed to be an important way of generating protein diversity by codon alteration in mRNAs. However, most of the editing sites are located in non-coding sequences. As outlined above, A-to-I RNA editing in non-coding sequences is an important regulator of gene expression. Editing in the mRNA non-coding sequences can affect gene expression by nuclear retention, translation regulation, mRNA degradation, and alternative splicing. In addition, editing can influence the processing or function of miRNAs, siRNAs, and lncRNAs, thus it would affect gene expression, which is regulated by miRNAs, siRNAs, or lncRNAs.

Although there is a strong interplay between A-to-I RNA editing and regulation of gene expression, several outstanding questions need to be addressed.

Is nuclear retention a general regulation method for hyper-edited RNAs? Although CTN-RNA, *Nicolin 1*, and *Lin28* mRNA were reported to be stored in nuclear paraspeckles, several results also show hyper-edited RNAs located in the cytoplasm. Thus, the same condition (hyper-edited) can lead to different fates (retained in nucleus or exported to cytoplasm). What are the key factors in this regulation? Maybe solving this question will enable us to elucidate the function of editing in nuclear retention.

Is Tudor-SN a nuclease for the inosine RNA? There are two findings regarding Tudor-SN: One result shows it is a nuclease, another indicates it is an enhancer. Whether Tudor-SN itself is a nuclease or promotes degradation with another factor should be determined in the future. Recently, ADAR1 and Tudor-SN were shown to locate in cytoplasmic stress granules following stresses [81]. This suggests ADAR1 and Tudor-SN may regulate RNA degradation by editing under stress condition.

Is there a correlation between edited non-coding RNAs and human disease? By deep sequencing, many editing sites are found in the non-coding RNAs in the human transcriptome. However, there are only a few cases showing that editing can influence miRNA or siRNA biogenesis and target recognition, and the function of edited lncRNAs is still unclear. Moreover, non-coding RNAs are associated with cancer [13–15], Prader-Willi syndrome [16,17], autism [18,19], and Alzheimer's disease [20], but no evidence shows that edited non-coding RNAs are related to human disease. ADARs are highly expressed in brain tissue, thus edited non-coding RNAs most likely play a regulatory role in brain development, functional diversification, and neurological disease. The function of edited non-coding RNAs in disease should be determined in the future.

This work was partly supported by the National Natural Science Foundation of China (31125011, 31071148, 31270844), the Doctoral Foundation of Ministry of Education of China (20110101130012), and Postdoctoral Research Project of Zhejiang Province (BSH1302085).

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